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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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SKIN BLEACHING PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Establishment of a Monograph

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 358]

[Docket No. 78N-0065]

SKIN BLEACHING DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Establishment of a Monograph; Notice of Proposed Rulemaking

AGENCY: Food and Drug Admnistration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the counter (OTC) skin bleaching drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, is part of the Food and Drug Administration's ongoing review of OTC drug products.

DATES: Comments by February 1, 1979, and reply comments by March 5, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fisher Lane, Rockville, Md. 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: Pursuant to part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on December 12, 1977 a report of the Advisory Review Panel on OTC Miscellaneous External Drug Products. On April 17, 1978, the Panel made a technical change which is discussed later in this document. (See part II. paragraph A.1. below—Introduction.) In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC skin bleaching drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; and (3) the conclusions and recommendations of the Panel to the Commissioner. The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address given above).

This report is the first of several to be issued by this Panel. This report pertains to products claimed to lighten dark pigment in the skin. Future reports by this Panel will cover other drug product categories described and published in the FEDERAL REGISTER notices of November 16, 1973 (38 FR 31677) and August 27, 1975 (40 FR 38179).

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report; the Panel's findings are being issued as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. The report has been prepared independently of the Food and Drug Administration (FDA). It represents the best scientific judgment of the members but does not necessarily reflect the agency position on any particular matter contained in it. After careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to established a monograph for OTC skin bleaching drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC skin bleaching drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after December 4, 1978, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests of confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510), (address given above).

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (category I), be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (category II), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. In the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), the Commissioner published the final regulations providing for the OTC drug review under § 330.10 which were made effective immediately. Pursuant to these regulations, the Commissioner issued in the FEDERAL REGISTER of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requests for data and information on all active ingredients utilized in OTC miscellaneous external drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report pursuant to § 330.10(a)(1) on the safety, effectiveness, and labeling of those products:

William E. Lotterhos, M.D., Chairman
Rose Dagirmanjian, Ph. D.
Vincent J. Derbes, M.D. (resigned July 1976)
George C. Cypress, M.D.
Yelva L. Lynfield, M.D. (appointed October 1977)
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Chester L. Rossi, D.P.M.

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings were held on February 23 and 24, April 20 and 21, June 27 and 28, August 15 and 16, September 28 and 29, November 9 and 10, 1975; January 18 and 19, February 20 and 21, April 2 and 3, May 16 and 17, July 11 and 12, October 8 and 9, November 12 and 13, 1976; January 14 and 15, February 27 and 28, April 3 and 4, June 5 and 6, June 25, August 5 and 6, September 30, October 1, and December 11 and 12, 1977.

Two nonvoting consultants, Albert A. Belmonte, Ph. D. and Jon J. Tanja, M.S., R. Ph., served on the Panel beginning in February 1977.

Four nonvoting liaison representatives served on the Panel. Marvin M. Lipman, M.D., nominated by an ad hoc group of consumer organizations, served as the consumer liaison. Gavin Hildick-Smith, Ph. D., who served as industry liaison from January until August 1975, and Bruce Semple, M.D., who served as industry liaison from August, 1975 until June, 1978, were nominated by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and

Fragrance Association, also served as an industry liaison.

The following FDA employees served: John M. Davitt, served as Executive Secretary until August 1977, followed by Arthur Auer. Thomas D. DeCillis, R. Ph., served as Panel Administrator until April 1976, followed by Michael D. Kennedy. Joseph Hussion, R. Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or the Panel's request on all drug categories under review:

Phillip R. Brachman, D.P.M.
Billy C. Coats, R. Ph.
David L. Cram, M.D.
Stanley I. Cullen, M.D.
R. Sherman Detrick
Chester DeZeih
Frank E. Dunlap, M.D.
Eugene M. Farber, M.D.
Beverly W. Foster
Dietrich Hoffman, Ph. D.
M. Kaminsky
Adam Kara, D.P.M.
Renate Kimbrough, M.D.
Leslie M. Lueck, Ph. D.
Robert Menzer, Ph. D.
William Mueller
Sigfrid A. Muller, M.D.
M. W. Rosenthal
Robert Scheuplein
Frederick Urbach, M.D.
Peyton E. Weary, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and the various data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through December 12, 1977, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC skin bleaching drug products are set out in three categories:

Category I. Conditions under which OTC skin bleaching drug products are generally recognized as safe and effective and are not misbranded.

Categroy II. Conditions under which OTC skin bleaching drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel did not classify any conditions for OTC skin bleaching drug products in category III.

I. Submission of Data and Information

The agency, in a attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, complied a list of ingredients found in OTC skin bleaching drug products through either historical use or from currently marketed products. Seven ingredients were identified as follows: Ammoniated mercury, ginseng, glycerylparaminobenzoic acid, hexachlorophene, hydroquinone, iodochlorhydroxyquin, and oxyquinoline sulfate. Notices were subsequently published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients as used in OTC skin bleaching drug products.

A. Submissions by Firms

Pursuant to the above notices, the following firms made submissions related to the indicated products:

Firms and Marketed Products

Chattem Drug & Chemical Co., Chattanooga, Tenn. 37409, Ultra Nadinola Cream, Deluxe Nadinola Complexion Cream, Derma Blanch, Nadinola Double Care Lotion.

Nicholas Products Ltd., Slough Bucks, England SLI 4AU, Ambi Skin Cream.

Plough Inc., Memphis, Tenn. 38151, Atra Skin Tone Cream.

USV Pharmaceutical Corp., Tuckahoe, N.Y. 10707, Esoterica Regular, Esoterica Facial, Esoterica Fortified, Esoterica Lotion, Esoterica Special, Golden Peacock Bleach Cream.

B. Labeled Ingredients Contained in Marketed Products Submitted to the Panel

Amyl dimethyl-PABA
Glyceryl-PABA
Hydroquinone

C. Additional Ingredients Considered by the Panel for Which No Data Were Submitted

Ammoniated mercury
Ginseng
Hexachlorophene
Iodochlorhydroxyquin
Oxyquinoline sulfate

D. Classification of Ingredients

1. *Active ingredients:*

Ammoniated mercury
Hydroquinone

2. *Inactive ingredients:*

Ginseng
Hexachlorophene
Iodochlorhydroxyquin
Oxyquinoline sulfate

3. *Ingredients deferred to other OTC advisory review panels or other experts:*

Amyl dimethyl-PABA
Glyceryl-PABA

E. OTC Volume Submissions

All "OTC volumes" refer to the submissions made by interested persons pursuant to the call for data notices published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). The volumes will be put on public display after December 4, 1978, in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

II. Skin Bleaching Drug Products

A. General Discussion

1. *Introduction.* As part of its review, the Panel was charged to evaluate data and information on the safety, effectiveness, and labeling of OTC skin bleaching drug products. The Panel reviewed submissions from four pharmaceutical companies.

The Panel has evaluated the only claimed active ingredient that was contained in all the products submitted for review. That single active ingredient was hydroquinone. The call for data by FDA listed seven active ingredients, one of which was hydroquinone. The remaining six ingredients were not present in any product submitted for review.

The Panel finds that these products are designed to bleach or otherwise lighten limited areas of hyperpigmented skin through a direct effect on the structure and function of the body, i.e., by the suppression of melanin pigment formation within skin cells. The Panel has classified all products of this type as drugs because the skin can be bleached or lightened, a desirable effect in many circumstances and conditions, only by a direct effect on the melanin pigment within skin cells, and because this effect is generally accomplished by the suppression of specific enzyme activity within the cell.

One company's line of products contained hydroquinone combined with sunscreen agents. These sunscreen agents were deferred to the Advisory Review Panel on OTC Topical Analgesic Drug Products, including Antirheumatic, Otic, Burn, Sunburn Prevention and Treatment Drug Products.

Skin bleaching drug products are intended to bleach or otherwise lighten limited areas of hyperpigmented skin. This effect should be noticeable in the majority of users within 2 months. The substance should not permanently injure the skin or produce systemic toxicity to the user. The Panel found hydroquinone to be safe and effective ingredient when used under the conditions specified. (See part II. paragraph B.1. below—category I labeling.)

Hyperpigmentation may result from a variety of causes. Endocrine imbalances such as Addison's disease, Cushing's disease, hyperthyroidism, pregnancy, or estrogen therapy will affect skin pigmentation. Metabolic alterations affecting the liver such as hemochromatosis, biliary cirrhosis, certain glycogen storage diseases, and

porphyria cutanea tardea are often associated with a diffuse melanosis. Rheumatoid arthritis has also been associated with alterations in pigmentation. Certain antineoplastic drugs such as busulfan, cyclophosphamide, and procarbazine have been known to produce a melanosis. Chlorpromazine in chronic high dosage and some antimalarials, such as chloroquine and hydroxychloroquine, have also been implicated. These drugs are known to have an affinity for melanin. Nutritional deficiencies such as kwashiorkor and sprue as well as vitamin deficiencies of niacin and cyanocobalamin may occasionally produce melanosis. Physical trauma to the skin such as friction, heat, various actinic radiations, allergic, sensitizers, photosensitizers, infectious agents, and many other factors which contribute to an inflammatory dermatitis may also contribute to a postinflammatory pigmentation (Ref. 1).

OTC skin bleaching drug products are useful in certain hyperpigmentation conditions that are benign and amenable to self-medication, such as melasma (the mask of pregnancy), freckles, and senile lentigines ("liver spots" and "age spots"). These conditions are troublesome or cosmetically unappealing to the patient, but are not symptoms of an underlying pathological condition requiring initial diagnosis and subsequent monitoring by a physician. For example, melasma, also known as chloasma, is a condition in which blotchy patches occur on the face, due to a hormonal imbalance caused by pregnancy or oral contraceptives. These blotches occasionally coalesce to form the "mask of pregnancy" (Ref. 2). Senile lentigines appear on sun-exposed areas of the skin at the menopause or male climacteric, but are not indicative of any hormonal disorder.

Because there is no literature to support use of skin bleaching drug products in children, the Panel concludes that they should not be recommended for use on children under 12 years of age.

The Panel concludes that several weeks of treatment are required for depigmentation. The Panel further concludes that sun exposure is to be avoided by the use of a sunscreen agent, a sun blocking agent, or protective clothing if pigmentation is not to reoccur (Refs. 3 and 4). Thus, the Panel recommended including the following warning in the labeling for skin bleaching drug products, "Use of a sunscreen on treated areas of the skin should be continued indefinitely in order to prevent darkening from reoccurring." During their April 17, 1978, meeting, the Panel was asked by the agency to clarify this warning. After considerable discussion the Panel voted to amend the warning to read as follows: "WARNING: Sun exposure should be avoided indefinitely by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin in order to prevent darkening from reoccurring."

The Panel concluded that this warning was the most important warning for skin bleaching drug products and recommended that it appear as the first warning on package labeling and that it be conspicuously boxed and in red letters. The discussion of this change was recorded in the minutes of that meeting (Ref. 5).

2. *Ingredients reviewed in addition to sumitted data.* The Panel, in addition to reviewing the submitted ingredients, reviewed all other ingredients listed in the agency's notice published in the FEDERAL REGISTER of August 27, 1975, calling for data and information on ingredients used in skin bleaching drug products for potential skin bleaching activity.

Hexachlorophene is listed in the current "United States Pharmacopeia" as a topical anti-infective (Ref. 6). The Panel has been unable to locate data and information on the the use of hexachlorophene as a skin bleaching agent.

Iodochlorhydroxyquin was listed in the "United States Pharmacopeia XVIII" (Ref. 7) and the "National Formulary XIII" (Ref. 8). The "Merck Index IX" and "Remington's Pharmaceutical Sciences XV" also list iodochlorhydroxyquin as a topical anit-infective (Refs. 9 and 10). Again, no mention is made of its use as a skin depigmenting agent.

Oxyquinoline sulfate, also known as 8-quinolol sulfate, oxine sulfate, 8-hydroxyquinoline sulfuric acid salt, quinosol, and chinosol, is listed in the "Merck Index" and "Remington's Pharmaceutical Sciences" as a topical anti-infective. It has been used as an antiseptic, antiperspirant, and deodorant, but no mention is made of skin bleaching properties (Refs. 11 and 12).

The Panel concludes that these ingredients have been incorporated in various skin bleaching preparations as pharmaceutical aids, i.e., preservatives.

Ginseng is not listed in any of the current compendia and the Panel has been unable to locate data and information relevant to its use in OTC skin bleaching drug products.

3. *Advertising.* The Panel's approval of an active ingredient or combination of active ingredients for a particular indication should not be interpreted as unique to the active ingredient or to the combination. Labeling, package inserts, or advertising should not refer to such approval either directly or by inference as a unique or an exclusive endorsement of such an ingredient or combination of ingredients.

The Panel is aware that the FDA does not regulate the advertising of OTC drug products. However, the Panel recommends that advertising for these drugs in any medium be consistent with the labeling claims in the proposed monograph. It follows that labeling and advertisements should, therefore, be closely monitored by the proper authority to ensure that advertisements do not go beyond the limitations of the monograph and/or negate restrictions and warnings recommended by the Panel.

REFERENCES

(1) Lorincz, A. L., "Disturbances of Melanin Pigmentation," in "Dermatolgy", edited by Moschella, S. L., D. M. Pillsbury, and H. J. Hurley, W. B. Saunders Co., Philadelphia, 1975.

(2) "Dorland's Illustrated Medical Dictionary," 25th ed., W. B. Saunders Co., Philadelphia, p. 928, 1974.

(3) Findlay, G. H., J. G. L. Morrison, and I. W. Simson, "Exogenous Ochronosis and Pigmented Colloid Milium from Hydroquinone Bleaching Creams," *British Journal of Dermatology*, 93:613-622, 1975.

(4) Arndt, K. A., and T. B. Fitzpatrick, "Topical Use of Hydroquinone as a Depigmenting Agent," *Journal of the American Medical Association*, 194; 177-119, 1965.

(5) Minutes of the Advisory Review Panel on OTC Miscellaneous External Drug Products, April 16-17, 1978.

(6) "The United States Pharmacopeia," 19th Revision, the United States Pharmacopeial Convention, Inc., Rockville, Md., p. 230, 1975.

(7) "The United States Pharmarmacopeia," 18th Revision, The United States Pharmacopeial Convention, Inc., Bethesda, Md., p. 338, 1970.

(8) "The National Formulary," 13th ed., American Pharmaceutical Association, Washington, D.C., p. 373, 1970.

(9) "The Merck Index," 9th ed., Merck & Co., Inc., Rahway, N.J., p. 664, 1976.

(10) "Remington's Pharmaceutical Sciences," 15th ed., Mack Publishing Co., Easton, Pa., p. 1093, 1975.

(11) "The Merck Index," 9th ed., Merck & Co., Inc., Rahway, N.J., p. 644, 1976.

(12) "Remington's Pharmaceutical Sciences," 15th ed., Mack Publishing Co., Easton, Pa., p. 1103, 1975.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which skin bleaching active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Category I Active Ingredient

The Panel has classified the following skin bleaching active ingredient as safe and effective and not misbranded:

Hydroquinone. The Panel concludes that hydroquinone is safe and effective for OTC use as a skin bleaching drug product as specified in the dosage and labeling sections below.

Hydroquinone is one of a group of three isometric dihydroxybenzenes, in which the two hydroxyl groups are para to each other, that is in the 1, 4 positions (Ref. 1). The traditional method of manufacture involves the oxidization of aniline to quinone with manganese dioxide, followed by reduction of the quinone to hydroquinone with metallic iron and water. Commercial variations have been used in which alkaline permanganate was used as the oxidant, and several variations of the reduction step have been reported. A radically new route has been attributed to a United States petroleum refiner, involving a direct parallel to the now well-proven cumene hydroperoxide route to phenol. In this instance the intermediate is 1,4-diisopropylbenzene, which is subjected to peroxidation and cleavage, yielding the desired hydroquinone product and acetone (Ref. 1).

Hydroquinone is extensively used as a photographic developer and in various processes which require an antioxidant. The derived antioxidants are particularly effective in preventing rancidity in fats and, therefore, find widespread use in foodstuffs. Miscellaneous applications in medicinals and dyestuffs account for about 20 percent of the total production of hydroquinone. Various derivatives of hydroquinone, mostly ethers, such as hydroquinone monomethyl ether, dimethyl ether, aminohydroquinone, dibutyl ether, and di(betahydroxyethyl) ether are articles of commerce. Other hydroquinone derivatives include such compounds as ditert-butyl hydroquinone. In general, the hydroquinone derivatives find utility through the oxidation-reduction reactions involving the reversible shift from the hydroquinone to the quinone configuration. In aqueous solutions this reaction is both rapid and quantitative, comparable to the reactions between ferrous and ferric ions (Ref. 1).

The raw materials from which hydroquinone is manufactured are processed by gravity under heat and pressure through various mixing and distilling vats, filter presses, and weighing machines, and the pure compound emerges in the packing room. Although ventilation is provided and the system is enclosed, fumes and dust particles escape into the atmosphere of the plant and produce lesions (Ref. 2). These lesions are described below. (See pt. II. par. B.1.(1) below—Safety.)

(1) *Safety.* In chronic toxicity studies, Stern, Lang, Brewer, and Carlson (Ref. 3) reported the effects of hydroquinone in "3 groups of 40 rats each of which were fed varying amounts of hydroquinone with citric acid and compared with a control group. After 2 years on test, 7 control rats, 10 rats fed 0.1 percent hydroquinone plus 0.01 percent citric acid, 11 rats fed 0.5 percent hydroquinone 0.01 percent citric acid, and 20 rats fed 1 percent hydroquinone plus 0.01 percent citric acid were still alive" (Ref. 3). The data on body weight, tibial length, WBC, RBC, and differential count revealed no significant differences among the groups, indicating no toxicity at these levels.

Lang, Brewer, and Carlson (Ref. 4) studied 19 adult human volunteers. Two men ingested 500 milligrams (mg) of hydroquinone daily for 5 months, 11 men and women ingested 300 mg daily for 5 months, and an additional 3 subjects ingested 300 mg daily for 3 months. Periodic blood and urine analyses were made throughout the duration of the experiments. None of the subjects showed any toxicity during the course of the experiments, and in no case did the analyzed data deviate significantly from accepted human norms.

In December 1975, Findlay, Morrison, and Simson in South Africa (Ref. 5) reported the development of ochronosis and pigmented colloid milium from hydroquinone bleaching creams. Hydroquinone creams are reportedly much sought after by South African black women. The effectiveness of hydroquinone creams was tested on South African black women seeking to bleach their skin. The author took pictures and compared the bleached face with the untreated natural dark brown of the neck or dorsal surface of the hand.

In this study, the authors noted that the facial epidermis overcame the bleaching effect during treatment and might grow darker than normal, particularly over sun-irradiated areas. The darkening tended to be most intense over those parts where the cream had been rubbed in well. Thereafter, novel changes developed in the papillary dermis. The dermal layer became ochronotic, with colloid degeneration and colloid milia production. These alterations could be observed in treated skin, parts of which retained a bleached appearance, though as a rule the initial bleaching effect of the cream was lost. Some manufacturers have included a sunscreen in the cream, but for those patients who were in the sun much the incorporation of the sunscreen did not prevent the deeper changes in the papillary dermis.

The striking development of the pigmented colloid milia in which the face has spots the size and color of caviar was first recognized by Alan Menter as cited by Findlay, Morrison, and Simson (Ref. 5). Analyses of the bleaching creams involved revealed that they contained approximately 5 percent and more of hydroquinone. In 6 of 35 patients, a blue tint was observed in the cavity of the external ear, due to ochronosis.

In patients reexamined after a year or more, the dermatosis was not significantly altered. Some improvement may have resulted from termination of treatment with the products, or from the use of a sunscreen by day and a steroid cream at night, but in general the changes were not strikingly reversed. In one case followed for 5 years, the milia were successfully removed with a skin graft knife, leaving a mildly hyperpigmented skin.

Forty-eight skin specimens were studied histologically. The main lesions occurred in the papillary layer of the dermis which showed foci containing ochronosis, elastosis, abnormal collagen with colloid degeneration, colloid milia pigmentary changes, telangiectasia with stretched plexus vessels around the tissue expansions, and sundry interstitial changes. Between the abnormal foci and below them there was no pathology, and epidermal changes were unspectacular (Ref. 5).

Ochronosis was common to all specimens in the study. The most striking ochronotic elements were broad stumpy fibers, parallel sided, curled or banana shaped, tending to transverse fracture, with jagged or pointed ends. Solar elastosis was often seen associated with ochronosis.

The interpretation was that the melanocytes had probably overcome the damaging influence of hydroquinone and were overactive. Prolonged application of the drug under conditions of sun exposure appears to lead in this result. Since changes in the dermis were not seen during the normal bleaching action of hydroquinone, the appearance of changes after melanocyte recovery suggested that the selective and damaging uptake of hydroquinone by melanocytes had ceased, and that the drug, with any of its chemical and metabolic derivatives, was then absorbed into the dermis (Ref. 5).

The Panel concludes that prolonged use of high concentrations (5 percent or more) of hydroquinone with exposure to the sun may produce disfiguring effects. These effects have not been reported at lower concentrations.

Arndt and Fitzpatrick (Ref. 6) reported that depigmentation from hydroquinone is limited and transient, while complete and progressive loss of pigmentation may occur from monobenzone (hydroquinone monobenzyl ether). In concentrations of 2 and 3 percent hydroquinone, no sensitivity reactions developed. An inflammatory reaction may develop after the first few weeks of treatment, but is often so mild that it may go unrecognized in heavily pigmented skin. The occurrence of inflammation makes subsequent lightening more likely. The re-

action is similar clinically to that which occurs during monobenzone treatment, but differs from the monobenzone reaction in that it has never been followed by a progressive loss of pigmentation due to destruction of the melanocytes. This study did not include the treatment of postinflammatory hyperpigmentation by following, for example, photosensitization reactions, lichen planus, or dermatitis caused by reaction to drugs. The use of hydroquinone for depigmenting the above conditions should never be considered without a cautious therapeutic trial on a limited, inconspicuous area. The earlier the treatment is begun with hydroquinone for depigmentation of minor skin blemishes, the more likelihood there is of a satisfactory cosmetic result. Repigmentation always occurred after treatment had been stopped. Darker lesions repigmented more rapidly than lighter lesions.

The Meirowsky effect (long wavelengths of ultraviolet light darkening melanin already present in the skin) may be a significant factor in reducing the effectiveness of hydroquinone depigmentation. Because of this, in practice it is recommended that the patient be advised to use a sunscreen cream or protective clothing during the day and hydroquinone ointment at night.

Arndt and Fitzpatrick (Ref. 6) prepared hydroquinone as a 2 or 5 percent cream which subjects applied twice daily. In most instances, only limited areas of a lesion were treated, i.e., half the face or one extremity. Only in this fashion could results be accurately documented for the patients served as their own control. Patients were examined at approximately monthly intervals. If no effect was discernible after 3 months, treatment was discontinued.

The use of 5 percent hydroquinone cream was accompanied by a high incidence of primary irritant reactions. At the lower concentration (2 percent cream), the drug appeared to be as effective; however, there were fewer side effects at the 2 percent than at the 5 percent concentration.

Decrease in skin color usually became noticeable after 4 weeks of treatment, but the rate of depigmentation was so variable that the time of onset of changes ranged from 3 weeks to 3 months.

Approximately four out of every five patients showed a skin lightening response to hydroquinone cream. Twelve percent of the patients were blacks; no difference was noted between their skin reaction and that of whites. Normal skin surrounding areas of vitiligo and abnormally pigmented skin such as that of melasma responded equally well. Before treatment, the lesions were bilaterally symmetrical. The patient's right cheek remained untreated throughout, while the cream was applied to the left cheek twice daily for 1 month. Subsequent exposure to ultraviolet light resulted in a return of normal pigmentation to the pretreatment level.

Few side effects were noted. Occasionally, patients complained of burning or stinging after applying the cream, and in some instances lesions became slightly darker before they faded. Three patients noted that their fingernails became temporarily discolored. In one instance, confetti-like depigmentation appeared over areas of melasma during treatment with hydroquinone. This patient had previously used hydroquinone monobenzyl ether. Thirty-two percent of the patients using 5-percent hydroquinone cream noted erythema and tingling at the site of application. Eight percent of those using 2 percent cream had similar reactions, but in none was the reaction severe enough to necessitate discontinuing the drug. In only one instance did the possibility of allergic sensitization arise. This patient's skin, which had previously reacted to 5-percent hydroquinone, was patch tested with both the 2 percent and the 5 percent cream. After 48 hours, the patch tests were positive and a generalized eczematous eruption had appeared.

Arndt and Fitzpatrick (Ref. 6) found that hydroquinone was a moderately effective depigmenting agent in 44 of the 56 cases they studied. When it was used in 2 percent concentration, the incidence of side effects was negligible. In one patient, a questionable leukoderma developed. The effectiveness of hydroquinone appeared to depend on the type of hypermelanosis and the cooperation of the patient. Patients were instructed to avoid sunlight, and during the summer months to use 15 percent para-aminobenzoic acid in a cream base to block the tanning of the skin. A major problem in preventing solar pigmentation remains, however, even after the usual sunscreens have been applied because the wavelengths that produce tanning and pigment-darkening extend into the visible spectrum. To block this spectrum, one would have to use a broad spectrum sunscreen such as an opaque sunscreen.

Hydroquinone cream did not lead to complete disappearance of the pathological hypermelanosis; evidence of the orignial pigmentary disturbance could ordinarily be discerned after its use. Results were satisfactory enough, however, to help most patients become less self-conscious about their abnormalities of melanin pigmentation.

In spite of the known pharmacological action of hydroquinone, workers exposed to large amounts do not become depigmented. Depending on the length of exposure, workers may show a reddish discoloration of hair and exposed skin, especially of the palms and soles (Ref. 6).

Velhagen (Ref. 7) found hydroquinone factory workers with lesions of the conjunctiva and cornea of varying degrees. He observed that if he placed a crystal of hydroquinone on filter paper previously saturated with alkaline tear drops, a brownish stain developed rapidly. He reasoned that small crystals of hydroquinone came in contact with the cornea and were there changed to paraquinone, which has the dark brown color. He also noted that paraquinone increased the pain threshold, permitting a greater exposure to the harmful agent without discomfort, thus setting up a vicious cycle.

In 1947, Anderson (Ref. 2) reported his observations on 41 workers in a hydroquinone plant. He and his coworkers found, in confirmation of Velhagen's observations, that the degree of loss of sensation is proportionate to the degree of staining of the cornea.

The changes seen in the eyes of the hydroquinone factory workers mentioned above would appear to be of two types, i.e., deposition of pigment in the conjunctiva and cornea, and opacification of the superficial portion of the cornea.

The deposit of pigment occurs in the form of spherules of various sizes. It is most prominent in the eyes of older patients and is to be observed in regions which normally contain fat, for example, in the palpebral portion of the episclera and in the arcus senilis of the cornea.

Development of the lesions as reconstructed from observations over a 2-year period would seem to be as follows (Ref. 2):

(i) The person comes into the plant and is trained to work in rotation in any of a half dozen stations. After a 2-year interval, a brownish tinge against the normally white sclera in the interpalpebral portions is noticeable. When examined with the slit lamp, the conjunctiva in these areas may appear slightly dried with a white, frothy, foamlike deposit attached irregularly and rather firmly to the surface. The deeper portions of the conjunctiva in the same interval assume the light brownish sepia stain. No true microscopic deposition of pigment in definite granules or globules is visible. The cornea remains clear.

(ii) After another 2- or 3-year interval, the conjunctiva appears more thickened and drier, and, in addition to the superficially placed white flecks and sepia stain, small, discrete, dark brown granules or globular precipitates are observed in the deeper structures, Some migration of pigment,

from the limbus into the cornea, can now be observed as well.

(iii) After 5 or more years of exposure, a definite increase is noted in the size, number, and spread of both the granules and the extent of staining. The cornea has now become gravely involved.

(iv) In the next stage, vision has become seriously reduced. The patient has been removed from contact with the chemical. The conjunctival staining has cleared, as it apparently does in time. The corneal staining decreases, but permanent damage is done to the cornea, resulting in increased opacity, increase in astigmatism, possibly corneal thinning, and keratoconus.

(v) The fifth stage may be the development of an opacity extensive enough to require a corneal transplant.

Two of Anderson's (Ref. 2) patients were hospitalized and subjected to exhaustive tests. Urinalysis and studies of the blood were performed repeatedly on all persons employed at the plant. The drug appears to be relatively harmless systemically; no systemic toxicity was observed in this study. As a matter of record, 12 grams (g) were ingested in one instance without fatality (Ref. 8). In this case, the urine gave a positive reaction for phenol for only 3 days after absorption of the drug, so that a positive reaction for phenol in Anderson's cases was hardly to be expected.

The Panel concludes that, although there are no reports of eye injury following the use of hydroquinone bleaching creams, contact with the eyes should be avoided.

In summary, the Panel concludes that 2 percent hydroquinone bleaching creams are safe over limited areas of the body. Their use has not been shown to produce significant systemic or local toxicity, and neither the eye damage reported with industrial exposure nor the skin damage reported with prolonged use of 5 percent creams has ever been reported with concentrations below 5 percent.

(2) *Effectiveness.* The search for an effective and safe agent that would cause depigmentation of human skin has long interested physicians and laymen. Abnormal variation in skin color not only constitutes a cosmetic liability, but in many instances produces formidable emotional and social problems (Ref. 6).

Hydroquinone was first reported to have depigmenting ability by Oettel (Ref. 9), who fed the drug to black-haired cats and noted that after 6 to 8 weeks their coats turned gray. Repigmentation of the hair occurred after the chemical had been withdrawn for a similar length of time. Martin and Ansbacher (Ref. 10) confirmed this work by feeding hydroquinone to young mice which developed achromotrichia within a period of 4 to 20 weeks.

Occupational leucoderma was reported in 1939 in black tannery workers. The responsible agent was found to be the hydroquinone monobenzyl ether, a rubber antioxidant present in gloves the workers had been wearing. These findings stimulated the investigation by Lerner and Fitzpatrick (Ref. 11) of the hydroquinone monobenzyl ether and similar compounds applied topically as depigmenting agents. It soon became apparent that the clinical use of this agent was associated with several serious difficulties. Its depigmenting ability was unpredictable, and irritation, sensitization, and leucomelanoderma at both treated and untreated sites became frequent problems. In the patients studied by Lerner and Fitzpatrick, leucoderma developed in 31 of 42 patients treated. Unfortunately, cessation of the agent's use did not necessarily stop the spread of depigmentation.

Hydroquinone itself has been shown to inhibit melanogenesis in vitro and in vivo (Refs. 12, 13, and 14). Topical application of hydroquinone produces a reversible depigmentation of skin and hair in humans, mice, and guinea pigs (Refs. 6, 12, and 15). It also produces a reversible regression of melanotic tumors in fish and mice (Refs. 15 and 16).

The mechanism by which melanin formation is inhibited by *p*-hydroxy phenyl drivatives was studied by Denton, Lerner, and Fitzpatrick (Ref. 12). They found that hydroquinone could completely inhibit the enzymatic oxidation of tyrosine to 3, 4-dihydroxyphenylalanine (dopa). They suggested that the hydroquinone monobenzyl ether may be converted in the skin to hydroquinone, which would then inhibit the reaction. It was also suggested that both hydroquinone and the hydroquinone monobenzyl ether could act topically by reducing melanin to a lighter colored substance.

Studies by Spencer (Ref. 15) and by Becker and Spencer (Ref. 17) show that when hydroquinone depigmentation has occurred, the microscopic findings indicate that melanin production is reduced by about one-half. These findings support the clinical observation that depigmentation of the lighter lesions is more apparent than depigmentation of the darker ones.

More precise anatomical studies were performed by Jimbow, Obata, Pathak, and Fitzpatrick (Ref. 18). Black guinea pigs were used in this study. The backs were epilated, and applications were made of creams containing 2 and 5 percent hydroquinone for 6 days of each week. Biopsy specimens were obtained at intervals of 1, 2, and 3 weeks. These creams induced not only depigmentation but also inflammatory changes and thickening of the epidermis. Depigmentation was visible within 8 to 10 days and was maximum within 14 to 20 days. Rarely could total depigmentation of the skin be observed. Examination of epidermal sheets after incubation in methyl dopa showed a marked decrease in the number of dopa positive melanocytes proportional to the duration of the applications. There was not only a reduction in the number of melanized melanosomes and the number of actively functioning melanocytes, but most of the dendritic cells were devoid of any melanized melanosomes. Moreover, some of them showed poorly developed intracytoplasmic organelles. Ultrastructural changes indicative of some sort of cellular degeneration were also seen. The authors felt that some of the melanocytes were destroyed and discharged from the skin with the exfoliating scales. The melanosomes which had been transferred into the keratinocytes by the melanocytes also showed definite evidence of degradation. The inflammation consisted of histiocytes primarily, but there were also lymphocytes and polymorphonuclear leucocytes. The epidermis was thickened, particularly the granular layers. Desquamation was prominent and was often seen within 1 week after hydroquinone application. In contrast to the extensive melanocytic changes, the keratinocytes did not show any cellular degeneration. An earlier study, referred to by the authors (Ref. 18), suggested that the primary action of hydroquinone is directed at tyrosinase in the melanocytes. This selective inhibition of the enzyme affects melanogenesis in the melanocytes resulting in subsequent cessation of melanin formation and depigmentation, i.e., enzyme-mediated depigmentation. Additional studies, referred to by the authors (Ref. 18), revealed that the primary action of hydroquinone is on some essential subcellular components of vital metabolic processes of melanocytes with resultant cytolysis, i.e., nonenzyme-mediated depigmentation.

In order to study the role of hormones and certain chemicals (among them hydroquinone) on mammalian pigment cells, Hu (Ref. 19) employed mammalian pigment cell strains grown in tissue cultures. He employed, in this study, pigmented (HFH-14 and HFH-18) and nonpigmented (HFH-18NP) cell strains derived from B16 transplantable mouse melanomas.

The melanoma cells were grown on coverglasses in Yerganian culture tubes. Controls and test cultures were fixed and stained at the end of 5 to 7 days of incubation and examined microscopically for extent of growth, rel-

ative numbers of pigmented and nonpigmented cells, and other cellular changes.

Other melanoma cells were grown in 2-ounce prescription bottles; 300,000 cells were inoculated into each culture bottle. In 7 to 9 days, compact sheets of cells were formed on the glass bottom, at which time the cultures were ready for subculture.

For subcultures, 0.01 percent trypsin in Hank's balanced salt solution was used to disperse the cells. When a cell suspension was obtained, a cell count was done to determine the extent of growth; 300,000 cells were then inoculated to another 2-ounce bottle to start the subculture.

For this study, at least three subcultures or more were done for each test agent. For each subculture, cytological examinations of stained as well as unstained slides were made.

At the end of 5 to 7 days of incubation, aggregates of pigmented cells were present overlying the nonpigmented cells in sheet formation on the glass surface. At this time, the coverglasses with the cells in monolayers were transferred and mounted in a perfusion chamber designed to accommodate the rectangular coverglasses. Motion picture sequences of these cells prior to treatment were made as controls, followed by sequences made immediately following treatment and overnight after treatment. In some, the medium containing the test agent was removed and replaced by normal growth medium. Sequences were made following this change of medium to see whether the cells could recover from the effect of the treatment.

All cultures were fixed at the end of the motion picture sequences, mounted on glass slides, and examined for evidence of cellular damage. The results were analyzed, and comparison was made between the treated and untreated cultures.

In general, it appeared that the pigmented cells were more susceptible to the effect of hydroquinone than the nonpigmented cells in the same culture. Following trypsinization, most of the pigment-containing cells disappeared. Only a few cells were seen in the fresh subculture in the first few days.

Hydroquinone inhibited growth of cells in vitro, particularly the pigmented cells, at a concentration of 0.625 micrograms per milliliter (μg/ml). When compared with control cultures, the hydroquinone-treated cultures grew much slower, less extensively, and with only a few pigment-containing cells, in contrast to the controls, which had many aggregates of pigmented cells. "When these treated cells were ready for subculture, the subcultures were also slow in growing and with a definite loss of pigmented cells. At concentrations of 1.25 and 2.5 μg/ml, hydroquinone inhibited growth completely when it was incorporated in the culture at the beginning of cultivation" (Ref. 19).

When the culture was well established in a normal medium, such as that used in the motion picture study, hydroquinone had no effect on the granule movement of the cells at 1 μg/ml, but it induced cessation of granule movement at 2.5 μg/ml. This effect was found to be reversible on certain occasions. In addition to its effect on the granule movement, hydroquinone also induced vacuolization of the cytoplasm and clumping of melanin granules. At 20 to 40 μg/ml, hydroquinone abruptly stopped granule movement in all cells in the same manner as a fixative affects cells.

Thus this study shows hydroquinone, in appropriate concentrations, exerts a skin-bleaching activity due to its injurious effect on the melanotic cells. A similar effect on goldfish pigment cells has been reported by Chavin and Schlesinger (Ref. 20).

Spencer (Ref. 14) appears to have been the first to use hydroquinone as a bleach, when he studied the chemical in 1961. The original study, although impressive, was felt to be limited because of the ease of oxidation of the hydroquinone in the ointment used. Once hydroquinone has oxidized, its effectiveness as a depigmenting agent is negligible. Oxidation was so pronounced when a 10 percent hydroquinone ointment was used that dark particles of oxidized hydroquinone in the ointment adhered to the skin. When lower concentrations, 1.5 and 2 percent hydroquinone, were used, depigmentation occurred even though yellowing of the freshly prepared white ointment developed within a few weeks. This discoloration of the 1.5 and 2 percent ointments would continue to increase until a dark gray color had developed. This color change was thought to be the result of oxidation of the available hydroquinone, making it worthless for therapy. After a more stable hydroquinone ointment was completed, reevaluation of hydroquinone in different concentrations was done.

Spencer (Ref. 15) reported observations of treatment with 2, 3, and 5 percent stabilized hydroquinone ointment for depigmentation of a variety of pigmentary changes. These included mainly freckles and lentigines occurring on the hands of middle-aged and older white men. Observations were also made on treatment of several black men in the same age group with normal skin.

The hydroquinone ointment being evaluated was applied to the back of one hand. The ointment base was applied to a similar area on the other hand. The treatment was continued twice daily for 3 months.

Depigmentation of lentigines with hydroquinone requires several weeks of treatment. In this clinical study, a plateau of depigmentation seemed to be reached at about the end of 2 months. Little or no change in color was observed during the final month of treatment. Whether or not further depigmentation would occur with prolonged therapy was not determined in this study. However, the number of patients in whom depigmentation developed from treatment with the stabilized hydroquinone was greater when compared with unstabilized hydroquinone preparations.

Depigmentation with hydroquinone may occur with or without a preceding inflammatory reaction. A transient inflammatory reaction developed in the majority of the patients in this study and lasted a week or so before any significant depigmentation occurred. Although inflammation may occur without depigmentation developing, its appearance during the course of treatment should not be considered an indication to stop therapy. The exception is the patient who develops an inflammatory reaction that increases in intensity. Here the possibility of sensitization should be considered. In the study, no patient being treated with 2 or 3 percent hydroquinone became sensitized. Two patients became sensitized while being treated with the 5 percent hydroquinone. Violent local reactions developed in these two patients and dissemination necessitated discontinuation of treatment. Patch tests with the original 5 percent hydroquinone ointment and another 5 percent hydroquinone ointment made after the reaction had cleared were strongly positive. The dermatopathologist who prepared and studied the biopsies reported that changes varied from acrokeratosis verruciformis to a lesion with long rete ridges that appeared almost anaplastic.

In blacks the response to hydroquinone treatment for depigmentation of normal skin is dependent upon the amount of pigment present. Only in the lighter skin was it possible to observe any contrast between the hydroquinone-treated hand and the control. No depigmentation was observed when darker skin was treated. Even when a clinical response was observed, the microscopic study failed to reveal any difference between the hydroquinone-treated and the untreated hand (Ref. 15).

The Panel concludes that there is ample clinical and laboratory evidence that hydroquinone in a concentration of 1.5 to 2 percent produces skin lightening effects in a majority of users.

The ease of oxidation of hydroquinone is an important factor in reducing

its effectiveness as a skin-lightening agent. With lower concentrations of hydroquinone, oxidation will not produce the pronounced discoloration of the ointment as with higher concentrations. Any darkening of the freshly prepared white ointment should be considered an indication of deterioration of the available hydroquinone.

One method of reducing oxidation has been to package hydroquinone ointment in small tubes. This minimizes the exposure of the ointment surface to air and limits the useable time of the opened package. Another method has been the use of a stabilizing agent such as sodium bisulfite.

(3) *Dosage.* Adult topical dosage is the thin application of a 1.5 to 2.0 percent preparation to the affected area twice daily. There is no recommended dosage for children under 12 years of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for skin bleaching active ingredients. (See pt. II. para. B.1. below—Category I Labeling.

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Category I Labeling

The Panel recommends the following category I labeling for skin bleaching drug products to be generally recognized as safe and effective and not misbranded.

a. *Indications:* (1) "For the gradual fading of 'age spots', 'liver spots', freckles and melasma (the mask of pregnancy, a condition of the skin that may also result from the use of oral contraceptives)."

(2) "Lightens dark pigment in the skin."

b. *Warnings:* (1) "WARNING: Sun exposure should be avoided indefinitely by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin in order to prevent darkening from reoccurring." This warning should be conspicuously boxed and in red letters.

(2) "Avoid contact with eyes."

(3) "If skin irritation develops, use of this product should be discontinued or a physician should be consulted."

(4) "If no improvement is seen after 2 months of treatment, use of this product should be discontinued."

(5) "Not recommended for use in children under 12 years of age."

(6) "Depigmentation (lightening) effect of this product may not be noticeable when used on very dark skin."

(7) *For products containing a combination of hydroquinone and a sunscreen:* "This product will bleach skin and is not for use for the prevention of sunburn."

2. *Category II conditions under which skin bleaching ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the category II conditions be eliminated from OTC skin bleaching drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

Category II Active Ingredient

The Panel has classified the following skin bleaching active ingredient as not generally recognized as safe and effective or as misbranded:

Ammoniated mercury. The Panel concludes that ammoniated mercury is not safe and not effective for OTC use as a skin bleaching drug product.

Ammoniated mercury, also known as ammoniated mercuric chloride, white precipitate, white mercuric precipitate, and aminomercuric chloride, is a water-insoluble substance, which was used in ointment form as a skin bleaching ingredient.

(1) *Safety.* Ammoniated mercury was used for many years as a skin bleaching ingredient until the hydroquinone monobenzyl ether became available.

Mercury can pass through the skin, especially in an ointment base, and chronic application can cause systemic mercury intoxication (Ref. 1). Sensitization is a common occurrence with these preparations according to Goodman and Gilman (Ref. 1) and Fisher (Ref. 2). For these reasons, the Panel feels that ammoniated mercury is not safe for OTC use as a skin bleaching agent.

(2) *Effectiveness.* The Panel has been unable to locate data relevant to the efficacy of ammoniated mercury in OTC skin bleaching drug products. The Panel concludes that ammoniated mercury cannot be generally recognized as effective.

(3) *Evaluation.* The Panel concludes that ammoniated mercury is not generally recognized as safe or effective. Moreover, the presence of a safe and effective ingredient (hydroquinone) renders the use of ammoniated mercury obsolete as a skin bleaching ingredient. The Panel consequently classifies ammoniated mercury as category II.

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Category II Labeling

The Panel has examined the submitted labeling for skin bleaching drug products and has classified the following claims as Category II:

a. *Certain labeling claims that are unsupported by scientific data and beyond the known pharmacologic*

properties of hydroquinone. These include all claims implying that the use of a skin bleaching agent results in healthier, younger, or rejuvenated skin. Examples of such claims include: "Helps skin look fairer, clearer, and younger"; "Helps fade the brown spots that tend to make your skin look older"; "Works in the pigment-forming cells of your skin to help fade those weathered brown spots on your neck and face—obvious blemishes which can make your skin look older than it should"; "Brightens, smooths, and softens skin"; "Gives a more even-tone wholesome looking coloring"; "Helps the aging changes in complexion to feel and look much younger."

b. *Claims which are not clinically defined or which would imply use of the product on injured skin or burns.* An example of such claims is "For stubborn cases where skin has become discolored, spotted, or darkened from bad weather or natural aging."

c. *Claims which use poorly defined terms that would confuse the consumer because the words have a different significance for different people.* Examples of such terms are "skin discolorations," "hand spots," "blotches," and "blotchy skin."

d. *Claims which imply an immediate rather than a gradual skin bleaching effect through use of certain terms.* Examples of such terms are "fast-acting," "quick," and "prompt."

e. *Claims which in any way negate, detract, or deemphasize the warning statements in Category I labeling.* (See part II. paragraph B.1. above—Category I Labeling.)

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* None.

C. DATA REQUIRED FOR EVALUATION

None of the skin bleaching active ingredients reviewed in this document for OTC use has been classified by the Panel as Category III. Therefore, studies to bring Category III skin bleaching active ingredients into Category I have not been developed by the Panel.

D. COMBINATION POLICY.

1. *General statement.* The Panel concurs with the OTC drug review regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

2. *Combinations of skin bleaching active ingredients.* The Panel has not developed a specific combination policy with respect to the use of more than one skin bleaching active ingredient in a formulation since only one safe and effective ingredient is known at this time, and the Panel sees little likelihood of any additional ingredients achieving general recognition of safety and effectiveness for this use in the immediate future.

3. *Combinations of hydroquinone with a sunscreen.* The Panel is aware of, and has had submitted to it, only one type of combination product, hydroquinone used with a sunscreen. The Panel concludes that this is a rational combination, since the depigmentation effect of hydroquinone is rapidly reversed by exposure to the sun. The Panel concludes that hydroquinone when used as a skin bleaching agent under the conditions set forth for category I ingredients may be combined with any category I sunscreen agent. However, the Panel feels that such a combination product must not bear indications for the prevention of sunburn and, in addition, must bear the following warning on its label: "This product will bleach skin and is not for the prevention of sunburn."

The Commissioner has carefully considered the environmental effects of this action and, because it will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended by adding new part 358, subpart A, to read as follows:

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—Skin Bleaching Drug Products

GENERAL PROVISIONS

Sec.
358.1 Scope.
358.3 Definition.

ACTIVE INGREDIENT

358.10 Skin bleaching active ingredient.
358.20 Permitted combinations of active ingredients.

LABELING

Sec.
358.50 Labeling of skin bleaching drug products.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371) (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—Skin Bleaching Drug Products

GENERAL PROVISIONS

§ 358.1 Scope.

An over-the-counter skin bleaching drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part 358, subpart A, in addition to each of the general conditions established in § 330.1 of this chapter.

§ 358.3 Definition.

Skin bleaching active ingredient. An agent designed to bleach or otherwise lighten limited areas of hyperpigmented skin through the suppression of melanin pigment formation within skin cells.

ACTIVE INGREDIENT

§ 358.10 Skin bleaching active ingredient.

The active ingredient of the product consists of the following when used within the dosage limits established: *Hydroquinone 1.5 to 2.0 percent.*

§ 358.20 Permitted combinations of active ingredients.

Hydroquinone identified in § 358.10 may be combined with any generally recognized safe and effective sunscreen active ingredient identified in § 352.10 of this chapter provided that the product is labeled only as identified in § 358.50.

LABELING

§ 358.50 Labeling of skin bleaching drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "skin bleaching agent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) *For products containing the ingredient identified in § 358.10 or any combination identified in § 358.20.* (i) "For the gradual fading of 'age spots,' 'liver spots,' freckles and melasma (the mask of pregnancy, a condition of the

skin that may also result from the use of oral contraceptives)."

(2) "Lightens dark pigment in the skin."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing the ingredient identified in § 358.10 or any combination identified in § 358.20.* (i) "WARNING: Sun exposure should be avoided indefinitely by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin in order to prevent darkening from reoccurring." This warning should be conspicuously boxed and in red letters.

(ii) "Avoid contact with eyes."

(iii) "If skin irritation develops, use of this product should be discontinued or a physician should be consulted."

(iv) "If no improvement is seen after 2 months of treatment, use of this product should be discontinued."

(v) "Not recommended for use in children under 12 years of age."

(vi) "Depigmentation (lightening) effect of this product may not be noticeable when used on very dark skin."

(2) *For combination products identified in § 358.20.* "This product will bleach skin and is not for use for the prevention of sunburn."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions" followed by "or as directed by a physician":

(1) *For products containing the ingredient identified in § 358.10 or any combination identified in § 358.20.* Adult topical dosage is the thin application of a 1.5 to 2.0 percent preparation to the affected area twice daily. There is no recommended dosage for children under 12 years of age except under the advice and supervision of a physician.

(2) [Reserved]

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the hearing clerk docket number found in brackets in the heading of this document) regarding this proposal on or before February 1, 1979. Such comments should be addressed to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be accompanied by a memorandum or brief. Comments replying to comments may also be submitted on or before March 5, 1979. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: October 17,1978.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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